Claims 1-17, 30-32 are pending in the subject application.

The specification stands objected to for allegedly adding new matter. The objectionable language has been deleted per Examiner's request. Withdrawal of the objection is requested.

Claim 5 stand objected to under 37 CFR §1.75(c) as allegedly of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 5 has been amended and is now an independent claim. Reconsideration and withdrawal of the objection is kindly requested.

Claims 31 and 32 stand rejected under 35 USC §112, first paragraph as allegedly containing subject matter which was not described in the specification as to reasonably convey to one skilled in the art that the inventors at the time the application was filed, had possession of the claimed invention. This objection is traversed in view of the following.

Claims 31 and 32 are drawn to DNA encoding a fusion protein comprising a *Yersinia pestis* F1 capsular antigen fused at its carboxyl terminus to an amino terminus of a V antigen from other *Yersinia* species having a V antigen homologous to *Yersinia pestis* V antigen such as *Yersinia pesudotuberculosis* and *Yersinia enterocolitica*. The

originally filed claims, specifically claim 24, describe a vaccine comprising a F1-V protein comprising the F1 capsular antigen of *Yersinia pestis* and V antigen of *Yersinia pestis*, or *Yersinia enterocolitica* V antigen or *Yersinia pseudotuberculosis* V antigen. This claim clearly shows that the applicants had conceived the invention at the time the application was filed. Further support is found on page 2 of the specification, lines 16-20 where the different species of *Yersinia* which have homologous V antigen are listed as *Yersinia pestis*, *Yersinia pseudotuberculosis*, and *Yersinia enterocolitica*. On page 13, lines 13-17 the vaccine of claim 24 is described again as comprising F1-V protein from a specific strain of *Yersinia pestis* and it could also contain V antigen from *Y. enterocolitica* and *Y. pseudotuberculosis*. The method of preparing such a vaccine "by inducing expression of a recombinant expression vector comprising F1-V protein sequence" is also described in this section.

In view of the above, claims 31 and 32 are sufficiently described in the application as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 11 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was

not described in the specification in such a way as to enable one skilled in the art to which it pertains to make or use the invention with regard to pF1V. Applicants acknowledge the withdrawal of this rejection with respect to claim 15. Upon Examiner's suggestion, Applicants will deposit plasmid pF1-V for patent purposes and will provide the deposit information when it is received.

Claims 1-10, 12-17 and 30-32 stand rejected under 35 U.S.C. §112, first paragraph as allegedly nonenabling and claims 1-10, 12-17 and 30-32 stand rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. These rejections are moot in view of the claim amendments. Withdrawal of the rejections is respectfully requested.

Claims 1-3, 5-17, and 30 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over WO95/18231 (Titball *et al.* -'31) and further in view of: WO 95/24475 (Titball *et al.*-'75); or Leary *et al.* *Infection and Immunity* **63**: 2854-2858, 1995). This rejection is traversed in view of the following.

As Examiner states in her rejection, previous fusions of F1 to β-galactosidase described in Titball *et al.*-'31, and fusions of V to glutatione-S-transferase described in Titball '75 and Leary et al. have been made and were found to be stable. These previous fusions were made with known and

tested fusion partners and do not provide any guidance to a person in the art as to how to produce a fusion of two antigens, one, F1 a surface protein, and V antigen, a secreted protein. Neither do the references provide any motivation to make such a fusion protein. As Examiner is aware, many parameters require consideration and testing when attempting a fusion protein, such as the site of fusion, the order of the proteins to be fused, whether the complete protein or antigenic portions of the proteins should be fused, whether enough protein will be expressed, whether the fusion protein will fold properly and retain antigenicity of the fused partners, among other considerations. The example provided with regard to the initial attempts of the Applicants to fuse the F1 antigen with an immunogenic portion of the V antigen (amino acids 168-275) was provided as an example of the uncertainty and undue experimentation required to produce a fusion protein which retains immunogenic characteristic of each of the fused partners. As discussed in the response of April 10, 1998, this initial attempt resulted in a fusion protein which was unable to effectively immunize mice against a subcutaneous challenge with F1$^-$ strain. In other words, the V fragment, a previously immunogenic peptide (please see Motin et al., 1994, *Infection and Immunity*, 62, 4192-4201, at "Abstract", last sentence, and throughout article. The article is attached as Exhibit A for Examiner's review), was no longer able to elicit a

protective response in the animal once fused to a portion of F1 protein. Please see the specification on page 22, lines 8-20 for a discussion of this F1-trucated V fusion protein.

Furthermore, the common knowledge of people in the art is that fusion proteins are unpredictable and do not follow any rules or principles. The article by E. Amann, The Utility of Fusion Proteins in the Development of Vaccines. In: Recombinant DNA Vaccines (R.E. Isaacson, ed. Marcel Decket, N.Y., 1992), discussed in the response dated April 10, 1998 is provided as Exhibit B for Examiner's perusal. The article discusses development of fusion proteins. As is mentioned on page 202 of the article under "Fusions to the N-terminus of β-Galactosidase", in the case of VP1 cDNA, two antigenic determinants were used, amino acid region 140-160 and amino acid region 200-213. When these antigenic determinants were fused individually to a β-galactosidase protein, each was properly expressed. However, when the two antigenic determinants were fused together, the resulting fusion protein did not properly induce antibodies reacting with food-and-mouth-disease virus (FMDV), probably due to improper three-dimensional folding of the fusion protein.

Since the references cited do not provide guidance for producing a F1-V fusion protein, and no rules or principles exist for making fusion proteins, undue experimentation would be necessary without high expectation of success. Hence, the cited art may render the invention, at best, "obvious to

try", but not obvious under U.S.C. §103(a). Therefore, none of the references, alone or in combination, render the invention obvious. Reconsideration and withdrawal of the rejection is respectfully requested.

All objections and rejections have been addressed. This application is believed to be in condition for allowance and Notice to that effect is requested.

Respectfully submitted,

By _____ Reg No 39,441
Elizabeth Arwine
Reg. No. P-45,867

U.S. A. MRMC
504 Scott Street
Fort Detrick, MD 21702-5012
ATTN: MCMR SGRD-JA (Charles H. Harris - Patent Atty)

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the

Commissioner of Patents
Washington, D.C. 20231

on June 29, 2000.

By _____
Sana A. Pratt
Reg. No. 39,441